REMARKS

Status Summary

Claims 1-96 are pending. Claims 1-73, 80, and 88 are withdrawn from consideration as being directed to a non-elected species. Claims 74-79, 81-87, and 89-96 were examined with the species of an anti-CD20 antibody. Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to enable practice of the invention based on perceived nonavailability / nonreproducibility of the RITUXAN® antibody. Claims 74-79, 81-87, and 89-96 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601a in view of Levy et al. (1994) *J Clin Invest* 93:424-428 and U.S. Patent No. 6,183,744 to Goldenberg et al.

New claims 97-102 are added. Reconsideration in view of the new claims and following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 81-82, 84, 86, and 90 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling practice of the invention. The examiner contends that it is uncertain whether the RITUXAN® (rituximab) antibody is known and publicly available and/or reproducible from the written description. Official action, page 3, item 7. This rejection is respectfully traversed.

Applicant respond that cells expressing the RITUXAN® (rituximab) antibody are publicly available as deposit number 69119 from the American Type Culture Collection. Further to the previously provide receipt of deposit, enclosed herewith is a letter from the ATCC dated January 7, 2004, which confirms that deposit number 69119 is publicly available. A representative of the ATCC further acknowledged via telephone that the inability to identify deposit number 69119 through their online catalog was a defect to be corrected by the ATCC.

In addition, the amino acid sequence of RITUXAN® (rituximab) is disclosed in U.S. Patent No. 5,736,137, which issued on April 7, 1998. Contrary to the examiner's assertion, the complete nucleotide sequence of the ATCC antibody is disclosed in the '137 patent. *See* Figures 3A-3F and SEQ ID NO:3, which provide the complete nucleotide and amino acid sequence of the C2B8 antibody in the TCAE vector. Applicant further submits that a skilled artisan could readily prepare anti-CD20 antibodies useful in the present invention given the

sequences of the heavy chain and light chain variable regions, as set for in Figures 4 and 5 of the '137 patent.

Based on the foregoing, this rejection of claims is believed to be rendered moot, and withdrawal of the rejection of claims 81-82, 84, 86, and 90 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Alas in view of Levy and Goldenberg

Claims 74-79, 81-87, and 89-96 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601A (Alas) in view of Levy et al. (1994) *J Clin Invest* 93:424-428 (Levy) and U.S. Patent No. 6,183,744 (Goldenberg). Official action, page 3, item 8. This rejection is respectfully traversed based on the arguments set forth below.

The examiner bears the burden of presenting a *prima facie* case for obviousness, with a showing of such *prima facie* obviousness requiring: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined references; and (3) a reasonable expectation of success. MPEP § 2143.

Alas teaches that the C2B8 antibody can be used to sensitize B cell lymphoma cells to cytotoxic agents. Alas observed that cells treated with C2B8 downregulate the expression of IL10. Based thereon, Alas postulated that the C2B8 antibody is effective based on regulation of IL10, which in turn regulates cellular apoptotic proteins. Levy teaches that IL10 enhances cell viability by inducing bcl-2 expression. This protective effect is abolished on addition of an anti-IL10 antibody. The use of an anti-IL10 antibody in Levy is limited to an IL10-induced cell protection. The examiner relies on Goldenberg as teaching multimodal therapies. In the view of the examiner, it would have been obvious to combine an anti-CD20 antibody with an anti-IL10 antibody because removal of IL10 abolishes the protective effects of bcl-2. Advisory action dated September 17, 2003, page 2.

The examiner has not established a *prima facie* case of obviousness because the Goldenberg reference, as well as other teachings in the art as of the filing date of the present application, *teach away* from the claimed combination therapy. Thus, the cited documents fail to teach, suggest, or motivate the claimed invention, and a skilled artisan would not expect to perform the claimed invention with any reasonable chance of success.

As stated previously, at the time of the instant invention, the use of IL10 antagonists in cancer therapy was controversial. The literature contained reports that both supported and discounted a correlation between cytokines and disease progression. The examiner has cursorily dismissed references that are clearly contrary to the examiner's position, and applicant respectfully requests that the examiner substantively consider the teachings of these documents.

With respect to the noted uncertainty in the art, the examiner has responded merely that "Bonnefoix has been addressed previously." Advisory action, dated September 17, 2003, page 2. The examiner previously stated that "Bonnefoix et al does not teach any IL10 antagonists and it is clear from the prior art in the rejection cited that IL10 is important for cancer therapy and regulates bcl-2." Official action, dated July 8, 2003, page 8, item 8. Bonnefoix et al. (1997) *Leuk Lymphoma* 25:169-178 (Bonnefoix) found that cytokines, including IL10, could either inhibit or stimulate proliferation of lymphoma cells of various histological subtypes. Applicant respectfully submits that an absence of teaching IL10 antagonists does not preclude the relevance of the reference. Based on Bonnefoix, which constitutes knowledge in the art prior to filing of the present application, it was unclear whether IL10 or an IL10 antagonist could be useful for cancer therapy.

Further with respect to the uncertainty in the art as to modulation of IL10 for cancer therapy, the examiner states that "Goldenburg teach multimodal therapy with anti-CD22 and chemotherapy. It is unclear how this teaches away from the invention." Advisory action, dated September 17, 2003, page 2. In addition to teaching use of an antibody that recognizes a B cell antigen, *i.e.* anti-CD22, in combination with chemotherapy, Goldenberg also describes treatment of B cell malignancies using an anti-CD22 antibody in combination with cytokines, such as IL10 (claim 15). Thus, Goldenberg teaches multimodal cancer therapies that include IL10, which is *directly opposite* to the claimed use of a multimodal therapy premised on inhibition of IL10. Although the examiner has relied on Goldenberg for the limited teaching of multimodal cancer therapies, it is improper to disregard the teaching of Goldenberg with respect to particular multimodal therapies related to use of IL10, which are most relevant to, albeit contrary to, the instant claims.

In addition, the examiner has not responded to applicant's previously submitted arguments with respect to U.S. Patent No. 5,770,190 to Bruserud (Bruserud). Similar to the methods of Goldenberg, Bruserud teaches that administration of IL10 (*not* IL10 antagonists as

presently claimed), optionally in conjunction with chemotherapeutic agents, for treatment of acute leukemia. Specifically, claim 1 of the '190 patent is directed to "[a] method for treating an acute leukemia in a mammal, comprising administering a therapeutically effective amount of interleukin-10 to said mammal."

Thus, the teachings of Alas, Levy, and Goldenberg, when considered alone or in combination, fail to motivate the use of an anti-CD20 antibody in combination with IL10 antagonists as recited in the instant claims. Further, the teaching of Goldenberg *teaches away* from the present invention. Similar references, including Bonnefoix, Goldenberg, and Bruserud, also *teach away* from use of IL10 antagonists for treatment of B cell malignancies, as now claimed.

Based on the foregoing arguments, applicant believes that claims 74, 76-79, and 83 are unobvious over the cited references in accordance with 35 U.S.C. § 103(a). Claims 75, 81-82, 84-87, and 89-96 ultimately depend from claims 74, 76-79, and 83 and are therefore also believed to be patentably over the cited references. Thus, applicant respectfully requests that the rejection of claims 74-79, 81-87, and 89-96 under § 103(a) be withdrawn.

Discussion of New Claims

New claims 97-102 are added, which specify use in the claimed methods of an anti-CD20 antibody comprising a heavy chain variable region of a C2B8 antibody, and a light chain variable region of a C2B8 antibody. Support for the new claims can be found in the originally filed specification, including at page 24, line 5, through page 25, line 5, wherein use of chimeric antibodies, such as antibodies having human constant domains and other humanized antibodies, is described; and at page 25, lines 20-21, wherein use of the C2B8 antibody is described.

At the time of filing the present application, a skilled artisan could prepare chimeric and humanized anti-CD20 antibodies with human effector functions according to the invention and without undue experimentation. *See e.g.*, Ruth D. Mayforth (1993) Designing Antibodies, Academic Press, Inc. San Diego, pp. 91-92 (copy enclosed). This text, available prior to the filing date of the instant application, summarizes genetic engineering approaches for preparing chimeric antibodies that include non-human variable regions and human constant regions. Mayforth also describes that constructs encoding chimeric antibodies can be modified to introduce mutations in the variable region gene segments that alter the binding affinity of the chimeric antibody for its target antigen. Thus, using standard molecular

biology cloning techniques, one could readily prepare anti-CD20 antibodies of the invention based on the disclosed sequences of anti-human CD20 variable regions and known sequences of antibody constant regions, including human constant regions.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP

Thomas A. Cawley, Jr., Ph.D.
Registration No. 40,944

P.O. Box 10500
McLean, VA 22102
(703) 905-2144 Direct Dial
(703) 905-2500 Facsimile

Date: September 13, 2004

TAC/JBM